Chapter 10

Endocrine Disorders

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I. INTRODUCTION

A. Patient **profile** and history. Endocrine diseases are recognized infrequently in large domestic animals (when compared with the incidence in their smaller, companion animal counterparts). A good history and physical examination is important in the diagnosis of endocrine problems. Endocrine disease should be considered whenever there are complaints of abnormal hair growth, water intake, or sweating.

B. Clinical findings. Endocrine dysfunction should be considered when the major problem is poor performance and after other conditions involving the musculoskeletal, respiratory, and cardiac systems have been ruled out.

C Diagnostic plan and laboratory tests. A routine complete blood cell count (CBC) and biochemical profile may be important to eliminate the involvement of other systems. Conversely, abnormal findings may lead the clinician to suspect pituitary or adrenal abnormalities. Specific hormone levels are helpful in some diseases. Cortisol findings are not valuable because of the large normal ranges in some domestic animals (e.g., horses). Endocrine function tests have been used in horses but rarely in ruminants.

II. DIABETES MELLITUS

A. Patient profile and history. This disease is rare in large domestic animals. When the disease does occur, the main complaints include polyuria, polydipsia, polyphagia, weight loss, and a strange sweet odor to the urine.

B. **Clinical** finding The affected animal may be thin with polyuria and polydipsia. Vital signs are normal.

C. Etiology and pathogenesis

1. Etiology
   a. Diabetes mellitus in the horse has been reported to be the result of a pituitary tumor and secondary to equine **Cushing's** disease. Therefore, this condition is not a true diabetes mellitus. Diabetes mellitus correctly refers to only those cases of hyperglycemia resulting from pancreatic islet β-cell deficiency, leading to a decrease or absence of insulin secretion.
   b. Pancreatic inflammation and destruction have been reported in both horses and cows as a cause of diabetes. *Strongyle* migration or localization of *Corynebacterium* species and Streptococcus *equi* have been implicated as causative organisms in horses.

2. **Pathogenesis**
   a. The specific stimulus for the release of insulin from β-cells is glucose. Insulin stimulates anabolic reactions, such as the synthesis of protein from amino acids, nucleic acid from mononucleotides, polysaccharides from monosaccharides, and lipids from fatty acids. Thus, a decrease in insulin results in disordered carbohydrate, protein, and lipid metabolism characterized by hyperglycemia and glucosuria.

b. Counter insulin substances (growth hormone, epinephrine, glucagon and cortisol) may contribute to the hyperglycemia by interfering with the action of insulin at the cellular level.

D. Diagnostic plan and laboratory tests. The clinical index of suspicion is raised by abnormal clinical chemistry findings on blood and urine. The diagnosis is confirmed by responses to insulin and glucose tolerance testing. An animal may have normal results on an insulin tolerance test and abnormal results on a glucose tolerance test.

1. Laboratory studies. In the few reported cases, there has been hyperglycemia (10–20 mmol/L), glucosuria, and ketonuria.

2. **Necropsy** results. In cows, pancreatic adenocarcinoma and infection related to the destruction of the pancreas may be evident at necropsy.

E. Differential **diagnoses**

1. Polyuria and polydipsia. Chronic renal failure may be ruled out by normal blood urea nitrogen (BUN) and creatinine. Urine-specific gravity is usually normal. Cushing's disease must be considered.

2. Hyperglycemia and glucosuria. Hyperglycemia of diabetes mellitus is usually greater than that associated with Cushing's disease. Additionally, hyperglycemia secondary to a pituitary tumor is generally insulin resistant, whereas hyperglycemia associated with diabetes mellitus is usually insulin responsive.

F. Therapeutic plan and **prognosis.** Treatment is rarely attempted. To maintain relatively normal blood sugar levels in the horse, 0.5–1 unit of protamine zinc insulin/kg twice daily, intramuscularly or subcutaneously has been used. The prognosis is grave because even with treatment, the long-term client compliance and patient response is poor.

III. DISEASES OF THE PITUITARY GLAND

A. Equine Cushing's disease

1. Patient profile. This condition is most common in aged horses (older than 12 years).

2. Clinical findings
   a. Vital signs are normal.
   b. Clinical signs. Owners complain of a shaggy hair coat even in summer, gradual weight loss, polydipsia, and polyuria.
      (1) **Hirsutism** may obscure signs of weight loss.
      (2) Polydipsia. The horse may appear "sway backed" or "potbellied" and may consume as much as 80 liters of water per day (normal consumption is 20–30 L/day).
      (3) Chronic infections and abscess development are common occurrences with this condition in horses. A common site is around the eyes and masseter muscles. Laminitis also is a common secondary finding and may be the presenting problem.
      (4) Neurologic **signs** may result from compression of the brain stem by a pituitary **tumor.**

3. Etiology and pathogenesis
   a. Etiology. The etiology of Cushing's disease in the horse is generally a tumor of the pituitary gland in the pars intermedia region. It has been stated that 75% of horses more than age 12 years have a pituitary adenoma at necropsy, but the majority of these do not exhibit clinical signs.
   b. Pathogenesis. Melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), β-endorphins, and corticotropin-like intermediate lobe peptide are produced by the pars intermedia. These substances often are increased in

horses with Cushing's disease. Increases in these substances probably result from an increase in a precursor molecule. The hypersecretion is insensitive to glucocorticoid negative feedback, which results in adrenal hyperplasia and increased cortisol levels. The elevated cortisol levels or possibly a lack of normal daily secretory rhythm results in hyperglycemia, polyuria, polydipsia, poor wound healing, and loss of muscle tone.

(1) Polyuria may be caused by an increase in the glomerular filtration rate (GFR) brought about by cortisol secretion. Cortisol may block either antidiuretic hormone (ADH) release or its action on the kidney. Secondly, an osmotic diuresis may occur because of glucosuria. Finally, compression of the posterior pituitary, hypothalamus, or both may cause lack of **ADH** release and result in polyuria.

(2) Polydypsia is secondary to polyuria and necessary to maintain hydration.

(3) Sweating (**hyperhidrosis**) occurs because of hypothalamic dysfunction or may be in response to the long hair coat.

(4) Muscle wasting and weight loss results from deranged carbohydrate metabolism caused by increased cortisol secretion and peripheral insulin resistance. The result is protein catabolism and gluconeogenesis.

(5) Infections, laminitis, and poor wound healing result from elevated cortisol levels.

(6) **Hirsutism** may be the result of androgens of adrenal origin.

4. Diagnostic plan and laboratory tests

a. Diagnosis relies heavily on laboratory tests. The total white blood cell count will be normal. There is usually an absolute or relative neutrophilia, lymphopenia, and eosinopenia (stress leukogram). Hyperglycemia is evident with blood glucose more than 6 mmol/L. Urinalysis reveals a glucosuria and ketonuria.

b. Plasma cortisol is high or normal. Interpretation of the findings must take into account the normal daily rhythm for cortisol secretion. In general, evening levels are usually two-thirds of morning values.

c. ACTH response test is exaggerated because of adrenal cortical hypertrophy. Basal levels of **ACTH** may be elevated in these cases and used as a diagnostic indication of disease.

d. Dexamethasone suppression test (**DST**). Endogenous cortisol is not suppressed by exogenous corticosteroid administration in affected horses because of autonomous secretion of **ACTH** by the pars intermedia tumor. This is the most reliable test.

5. Differential diagnoses

a. Chronic debilitation. Chronic weight loss and debilitation in an older horse may be caused by poor management and nutrition. A thorough examination of the mouth should be performed to eliminate dental or oral cavity problems. A fecal flotation should be performed to rule out parasitism. Any chronic systemic disease can result in debilitation (e.g., pulmonary or abdominal abscess, neoplasia, chronic renal/hepatic disease).

b. Polyuria and polydipsia. Chronic renal failure can be ruled out with BUN, creatinine, and urinalysis findings.

c. Hyperglycemia and glucosuria Diabetes mellitus caused by pancreatic islet β-cell deficiency is extremely rare in the horse. There are only a few published reports of diabetes mellitus that are truly diabetes mellitus; the other cases of diabetes mellitus have always been associated with a pituitary tumor and are resistant to insulin treatment.

6. Therapeutic plan

a. Cyproheptadine has been used with some success in horses with Cushing's disease. This drug has anticholinergic, antihistaminic, and antiserotonin activity and is thought to compete with serotonin for receptor sites. This may prevent serotonin-regulated **ACTH** release. The initial dose of 0.6 mg/kg orally once a day in the morning is increased to 1.2 mg/kg over several weeks. Improvement, if seen at all, usually occurs between 6 and 8 weeks. This drug may cause tranquilization, which, if severe, will force discontinuation of the medication.

b. A few reports of the use of **O,P'-DDD (Permax)** in pituitary adenomas have been published. These treatments were not successful, and the drug is expensive.
c. Pergolide, an ergot alkaloid, is being investigated in the treatment of pituitary adenomas. It is a dopaminergic agonist that causes intense vasoconstriction and vascular endothelial damage. This drug may be used at low dose levels (0.75 mg/day) until clinical signs improve and the DST returns to 25% of pretreatment values. Then the horse may be maintained at 0.25 mg/day. Alternatively, a higher dose (2.5–3.5 mg/horse/day) with a gradual decrease over time is advocated by some veterinarians.
d. Bromocriptine, also a dopaminergic agonist, has been used experimentally but is extremely expensive.

7. Prevention. Even without treatment, the animal may live for several years. Special care must be taken to minimize infections and laminitis and to provide a high plane of nutrition.

B. Diabetes insipidus

1. Patient profile and history. A few cases of diabetes insipidus have been reported in horses and food-producing animals. In these cases, the chief complaint has been the occurrence of polyuria and polydipsia in the animal.
2. Clinical finding. Because of a lack of cases, no set clinical signs are known. Polyuria and polydipsia are always present.
3. Etiology and pathogenesis
   a. Diabetes insipidus is characterized by polyuria and polydipsia in the absence of renal disease or glucosuria. The inability to concentrate urine may be because of a lack of synthesis or release of ADH or a blockage of ADH action on the renal tubules. ADH increases the levels of cyclic adenosine monophosphate (cAMP) in the renal tubule cells, leading to increased tubule cell permeability.
   b. This diabetes can be congenital or acquired, complete or partial. In humans, diabetes insipidus can result from pituitary adenomas, metastatic neoplasia, postpartum pituitary necrosis, and disseminated intravascular coagulation. In horses, a familial syndrome of diabetes insipidus has been described in sibling colts.
   c. If the animal responds to vasopressin, then a lack of ADH production from the hypothalamus or a lack of release from the neurohypophysis is the cause. Brain lesions that may result in this condition could be abscessation neoplasia or vascular disturbances.
4. Diagnostic plan and laboratory tests. The diagnosis is made based on the clinical findings and the following laboratory tests:
   a. CBCs and chemistry profiles are usually normal in these cases.
   b. Urinalysis is normal except for a low specific gravity [i.e., 1.002 and low osmolality (less than 300 mOsm/L)]. Serum osmolality is often increased (more than 300 mOsm/L).
   c. Vasopressin response test. Following the administration of vasopressin USP (100 units is given intramuscularly), the animal should begin to concentrate urine within 1 hour and should achieve peak concentration 4 hours post injection.
   d. Water deprivation test. Animals with diabetes insipidus are not able to concentrate urine in the face of dehydration.
5. Differential diagnoses
   a. Renal disease is ruled out by a normal BUN and creatinine.
   b. Psychogenic polydipsia and polyuria are eliminated on the basis of the water deprivation test. Animals with psychogenic drinking are able to concentrate urine if they become dehydrated unless medullary washout has occurred.
   c. Nephrogenic diabetes insipidus is not present if the animal responds to vasopressin.
   d. A tumor of the pars intermedia presents with polyuria and polydipsia in association with hyperglycemia and glucosuria.
   e. Partial or complete diabetes insipidus is differentiated by ADH assays and response to chlorpropamide.

6. Therapeutic plan. Therapy is seldom attempted in large animals. One case in a cow resolved spontaneously in a few months. The owner should be instructed to ensure an adequate supply of water for the animal at all times.
   a. In cases of partial diabetes insipidus, chlorpropamide, a hypoglycemic agent, can be used. This drug acts to increase intracellular cAMP, thereby accentuating the effects of ADH on renal tubule cells. This agent is ineffective in cases of complete diabetes insipidus.
   b. Pitressin tannate in oil is the ADH analogue most commonly used in veterinary medicine. This preparation is given intramuscularly and is often painful. Hypersensitivity and resistance can develop. The antidiuretic effect is often variable.
   c. Desmopressin, a newer ADH analogue, is used in humans, dogs, and cats. It has not been tried in large animals to date. This agent acts by binding to ADH receptors in the renal tubules, increasing cAMP and, thus, water permeability. The dosage is titrated to effect, and this drug is available for intranasal and parenteral use.

IV. DISEASES OF THE ADRENAL GLAND

A. Equine pheochromocytoma.

Pheochromocytomas are tumors resulting from the **chromaffin** cells of the adrenal medulla. These tumors may be functional or nonfunctional, malignant or benign. Most of these tumors are unilateral, although bilateral tumors can be found.

1. Patient profile and history. Pheochromocytoma has been reported mainly in horses. In most of the cases, the condition occurred in older animals (older than 12 years). There is no specific breed or sex prevalence.

2. Clinical findings. Vital signs may be increased, heart sounds may be loud on auscultation, and a bounding jugular pulse may be noted. The animal may appear anxious or overexcited. Hyperhidrosis and muscle tremors are prevalent signs. Pupils are dilated but responsive. Polyuria and polydipsia may be present.

3. Etiology and pathogenesis
   a. The neoplasm is usually benign and grows slowly, with local destruction of tissue being the only effect of the tumor. On rare occasions, the tumor may metastasize to related lymph nodes, liver, lung, and bone. Vascular penetration and invasion of the vena cava and aorta may sometimes occur.
   b. Functional tumors may cause an increase in norepinephrine and epinephrine secretion. The high epinephrine concentrations cause hyperglycemia and sweating. Gluconeogenic effects of the catecholamines, catecholamine-induced suppression of insulin secretion, and catecholamine-induced increase in plasma glucagon cause hyperglycemia. Excessive sweating can result in polydipsia. In humans, increased levels of norepinephrine cause hypertension. It is unknown if this occurs in animals.
   c. Compromised renal function may result occasionally and is believed to occur because of norepinephrine-mediated vasoconstriction, reducing renal blood flow. In humans, death usually results from cardiovascular collapse, presumed to be caused by muscular hypoxia secondary to vasoconstriction.

4. Diagnostic plan and laboratory tests
   a. A detailed physical examination should be performed, and a CBC and chemistry profile should be obtained. Hyperglycemia and glucosuria are the most likely laboratory findings.
   b. Catecholamine assays of blood and urine are used in humans. Catecholamines are extremely unstable and samples must be processed within minutes or the results are of no value.

5. Differential diagnoses
   a. Pituitary adenomas should be considered when the age of the animal and clinical picture fits the disease profile.
   b. Other conditions to be ruled out include causes of hyperglycemia, such as diabetes mellitus and equine Cushing's disease. Plasma cortisol levels, an ACTH response test, and a dexamethasone suppression test may help differentiate disorders.
   c. Pancreatic α-cell tumors are rare but do increase the secretion of glucagon and cause increased glyconeogenesis.

6. Therapeutic plan and prognosis. Treatment usually is not attempted in large animals because a diagnosis is not usually made antemortem. In humans, α-blockers, such as phentolamine and phenoxybenzamine hydrochloride, have been used to control blood pressure. Propranolol (a β-blocker) is used if an arrhythmia is present. Both blockers are effective in decreasing sweating and hypermetabolism. The preferred treatment in humans is a tyrosine analogue (α-methyl tyrosine), which inhibits the rate-limiting step in catecholamine production. The prognosis is grave in all cases.

B. Equine adrenal insufficiency

1. Patient profile and history. Race horses that have received glucocorticoid or anabolic steroid injections are possible candidates for this condition. Poor condition, poor performance, hirsutism, and lethargy are the complaints. Mares may exhibit anestrus.

2. Etiology and pathogenesis
   a. It has been found that only 2 mg of dexamethasone can suppress cortisol secretion for 24 hours in the horse. This implies that small glucocorticoid doses given once or twice a day in the form of anabolic steroid preparations or intra-articular injections may induce adrenal insufficiency. The incidence of Addison's disease (equine adrenal insufficiency) in the horse is unknown, but iatrogenic adrenal insufficiency should be considered in the diagnostic workup of poor performance horses.
   b. Mares who have received anabolic steroids while racing appear to go through a "letdown" period when they are retired from the track. It may be 6 months before they begin to put on weight Reproduction cycles may be interrupted.
   c. In research studies in which horses have been bilaterally adrenalectomized, the cause of death is severe hypoglycemia or severe electrolyte disturbances.

3. Diagnostic plan and laboratory tests
   a. Diagnosis relies on laboratory findings. Studies that have created bilaterally adrenalectomized horses have shown an increase in the packed cell volume (PCV), increased serum potassium levels, and decreased serum sodium, chloride, and glucose levels. Serum cortisol levels are low, and horses fail to respond to ACTH stimulation.
   b. Normal or depressed serum sodium concentration with a concurrent high-percentage creatinine clearance ratio of sodium in urine indicates salt wasting or hypoaldosteronism (Figure 10-1). Normal levels in the horse are 0.02%–1%.

4. Differential diagnoses
   a. Chronic weight loss caused by gastrointestinal involvement
   b. Chronic infection causing lethargy
   c. Lameness that may contribute to poor performance
   d. Cardiovascular disease
   e. Electrolyte disturbances

$$\frac{\text{Urinary Na}}{\text{Serum Na}} \times \frac{\text{Serum Cr}}{\text{Urinary Cr}} \times 100 = \%\text{CrNa}$$

FIGURE 10-1. Calculation of the creatinine clearance ratio of sodium (*% CrNa*). *Cr* = creatinine; *Na* = sodium.

5. Therapeutic plan and prevention
   a. Rest and reduction of stress usually helps mares adjust. If the results of an ACTH stimulation test are still abnormal after 3 months, glucocorticoid supplementation may be necessary.
   b. If **glucocorticoid** therapy is needed in the horse, then alternate-day therapy would reduce the incidence of iatrogenic adrenal suppression. If daily administration of steroids is needed, then the animal should be weaned off the drug gradually. This should be accomplished over 4–6 weeks by cutting the dose in half every fifth day until the last week, when alternate-day therapy is used.

V. DISEASES OF THE THYROID GLAND

A. Equine **hypothyroidism**

1. Patient profile and history. Hypothyroidism occurs rarely, but when it does occur, the disorder is seen most frequently in racehorses, obese mares, and foals. Racehorses present with poor performance, erratic appetite, decreased endurance, dullness, and stiffness of gait. Hypothyroid obese mares often have a history of recurrent laminitis and erratic reproductive function. Foals may be weak, stillborn, or have contracted tendons and tarsal bone collapse.

2. Clinical findings
   a. Foals. If hypothyroidism begins early in fetal development, the neonate fails to establish normal respiration at birth. Onset in late pregnancy produces a foal that is lethargic and unable to stand and suckle. In studies on surgically created thyroidectomized (THD) foals, the animals are stunted and may die in 1–2 months.
   b. Adults. Similarly, THD adults are lethargic, slow moving, have lower rectal temperatures than normal, and an intolerance to cold. They have scaly haircoats, delayed closure of epiphyseal plates, decreased libido, and edema of the distal limbs. This condition is not life threatening and the signs can be reversed with thyroid supplementation.
   c. Race horses. Hypothyroidism has been suggested in racing thoroughbred and standardbred horses that present with signs similar to "tying-up" syndrome (see Chapter 13 I B 2 a). These animals do not perform well, are stiff, and may exhibit the percussion dimple of pseudomyotonia.

3. **Normal** physiology
   a. **Iodine** absorbed from the gastrointestinal tract is combined with **tyrosine** in the thyroid gland to form **monoiodotyrosine (MIT)** and then diiodotyrosine **(DIT).**
   b. Thyroxine **(T_4)** is formed by couplingtwo DIT molecules, and **3,5,3' triiodothyronine (T_3)** is formed by the coupling of one MIT and one DIT molecule. T_3 and T_4 are stored in the follicular colloid in the thyroid gland and are released in response to TSH from the pituitary gland. It is currently thought that when T_4 enters a cell, it is converted to the biologically active T_3. The concentration of T_3 and T_4 are regulated by the negative feedback mechanism on the pituitary.
   c. Thyroid hormones affect most body tissues by acting on cells at the level of the nucleus, mitochondria, or plasma membranes. These hormones affect cellular metabolism through amino acid transport and oxygen consumption, both of which impact cellular growth, differentiation, proliferation, and maturation.
   d. Diurnal variations in T_4 and T_3 levels occur in horses. T_4 peaks in the late afternoon, with lowest levels in early morning. T_3 peaks in the morning, with lowest levels occurring around midnight. These variations need to be kept in mind when only a single sample is tested. Thyroid hormone levels also decrease with age; foals have twice the T_4 values of adults.

4. Etiology and pathogenesis
   a. Primary hypothyroidism may be caused by an idiopathic autoimmune disease.

b. Secondary hypothyroidism may be caused by a lack of thyroid-stimulating hormone (TSH) or TSH-releasing factor from the pituitary or an impaired transport of TSH. This condition may be seen in conjunction with pituitary adenomas of the pan intermedia.

5. Diagnostic plan and laboratory tests. Laboratory tests include a CBC, serum biochemistry, T_4 levels, TSH response test, and perhaps a thyroid biopsy. The diet should be evaluated to identify any agents known to affect the thyroid's iodine uptake (e.g., kelp).
   a. CBC and serum biochemistry. Abnormal laboratory findings include a normocytic, normochromic anemia. The PCV is in the mid 20s. Serum phosphorus may be decreased and probably relates to decreased feed intake.
   b. **T_4 levels.** Serum T_4 level is low (0.5 μg%; normal is 1–3 μg%). Because radioimmunoassay measures only bound T_4, drugs that compete for protein-binding sites (e.g., phenylbutazone, anabolic steroids) artificially lower T_4 values. Free T_4 levels are not affected by these drugs, and a horse may be euthyroid despite a low T_4 value.
   c. TSH response test. TSH (5 IU) is administered intramuscularly, and T_3 and T_4 levels are measured at 1–4 hours post treatment. A normal response would be a twofold increase in T_3 and T_4. An increase less than twofold is considered indicative of primary hypothyroidism.

6. **Differential diagnoses**
   a. In foals, consider metabolic bone disease, septic arthritis, contracted tendons caused by lameness, and osteochondritis dessicans.
   b. In racehorses, rule out rhabdomyolysis, lameness, polymyositis, or systemic disease.
   c. **Pituitary adenomas** must also be ruled out (see III A).

7. Therapeutic plan and prognosis. Sodium levothyroxine (10 mg) is administered orally in 70 ml of corn syrup daily. Measure T_3 or T_4 levels every 1–2 weeks, and adjust dosage as needed. The prognosis is good, but lifetime supplementation may be needed.

B. Goiter (iodine **deficiency**)

1. Patient profile and **history.** This condition is seen in newborn animals of all species and is worldwide in distribution.

2. Clinical findings. The major clinical findings are neonatal death with alopecia and visibly enlarged thyroid glands in surviving animals.

3. Etiology and pathogenesis
   a. Primary iodine deficiency. Iodine-deficient soils are common worldwide because of leaching of soils not replenished by the iodine found naturally in oceans.
   b. Diets rich in brassicas and other goitrogenic plants likely produce a thiocyanate in the rumen of ruminants, which may restrict the uptake of iodine by the thyroid. Iodine deficiency results in decreased T_4 production and stimulation of TSH secretion, resulting in hyperplasia of the thyroid gland. Clinical signs are the result of hypothyroidism. Iodine is an essential component for normal fetal development.

4. Diagnostic plan and laboratory tests. The diagnosis is made based on clinical findings, necropsy, and laboratory results. Diagnostic strategies include measuring iodine levels in the blood and milk of the herd or flock and obtaining serum T_4 levels.

5. Therapeutic plan. Surviving animals should receive iodine supplements. Overdosing can cause toxicity.

6. Prevention. Supplement diets with iodine as a salt or mineral mixture.

C. Equine **hyperthyroidism** is a rare condition but may be considered if presented with a high-strung, unmanageable animal.

D. Bovine ultimobranchial (thyroid C-cell) tumor

1. Patient profile and history. This condition is seen in older animals (age 6–20 years), usually bulls.
2. Clinical findings. There is slight palpable enlargement of the thyroid gland region caused by extensive multiple nodular enlargements along the ventral aspect of the neck. There is severe vertebral osteosclerosis with ankylosing spondylosis deformans and degenerative osteoarthrosis, resulting in clinical lameness in these bulls.
3. Etiology and pathogenesis. There is a possible association with long-term ingestion of a high-calcium diet. The chronic stimulation of the C-cells and ultimobranchial derivatives by high levels of calcium absorbed from the digestive tract may be related to the pathophysiology of the neoplasms. Cows do not develop proliferative lesions during similar dietary conditions because of the high physiologic requirement for calcium during lactation.
4. Diagnostic plan and laboratory tests. Fine needle aspiration of any masses should be performed. Radiographs should be taken of the thorax and spinal column. Serum calcitonin levels should be measured. Calcitonin levels may or may not be increased, and serum electrolyte levels are within normal range.
5. Differential diagnoses. C-cell adenomas grow slowly. C-cell carcinomas are larger and cause observable enlargements in the anterior neck region of older bulls and frequently metastasize to the anterior cervical lymph nodes and lungs.
6. Therapeutic plan. There is no known treatment.
7. Prevention. Avoid feeding high-calcium diets to bulls.

E. Equine thyroid tumors

1. Patient profile and history. The reported cases have been in horses older than age 8 years. The presenting complaint is swelling in the region of the larynx.
2. Clinical findings. There is a palpable mass in the area caudal to the larynx. The animal may be inclined to gulp excessively. Exercise intolerance may be a finding.
3. Normal physiology. The thyroid gland in the horse consists of a pair of encapsulated lobes that are symmetrically situated on either side of the trachea caudal to the larynx. They measure approximately 2.5 cm × 5 cm and are frequently palpable in the normal horse.
4. Etiology and pathogenesis
   a. Thyroid adenomas are common in older horses, but they are usually a postmortem finding.
   b. Thyroid carcinomas and C-cell tumors have been reported in the hone, but they are uncommon.
5. Diagnostic plan and laboratory tests. Fine needle aspiration of the mass, a T_4 test, and a TSH response test should be performed. Serum T_4 and TSH levels are variable. Endoscopy may be useful to rule out an upper airway problem. Thyroid scintigraphy may indicate abnormal uptake.
6. Therapeutic plan and prognosis. Surgical removal of carcinomas and C-cell tumors is necessary. Prognosis is good if no metastasis has occurred.

VI. DISEASES OF THE PARATHYROID GLAND

A. Primary hyperparathyroidism

1. Patient profile and history. This condition is seen in older horses (older than 15 years) but is rare.

2. Clinical findings. There may be lethargy, but there have been too few cases reported to generalize.

3. Etiology and pathogenesis
   a. Etiology. Primary hyperparathyroidism may be the result of parathyroid **adenoma,** parathyroid hyperplasia, or carcinoma. Few cases of parathyroid adenoma have been reported. This may be because the two pairs, or sometimes more than two pairs, of parathyroid glands are widely separated in the horse and are often difficult to identify.
   b. Pathogenesis. Primary hyperparathyroidism should always be considered in horses with hypercalcemia, particularly if it occurs in the absence of renal failure or neoplasia. When calcium levels increase dramatically, mineralization of soft tissues may occur, leading to renal and myocardial calcification and subsequent renal failure and arrhythmias. Death may follow.

4. Diagnostic plan. Serum and urine calcium, phosphorus, and parathyroid hormone (PTH) levels and the percentage creatinine clearance of phosphorus should be obtained.

5. Laboratory tests. The CBC is normal, but hypercalcemia and hypophosphatemia are evident. BUN and creatinine levels are usually normal. Urinalysis is normal, but there is an increased fractional urinary excretion of phosphorus (normal is 0%–0.5%).

6. **Therapeutic** plan and prognosis. Therapy rarely has been attempted or reported. Steroid therapy (prednisone) may be rational. Steroids act to decrease calcium absorption from the gastrointestinal tract, decrease release of calcium from bone, and increase urinary excretion of calcium. The prognosis is guarded to grave.

B. Nutritional secondary **hyperparathyroidism (NSH), osteodystrophia** fibrosa, big head disease, bran disease, Miller's disease

1. Patient profile and history. Although any age and breed may be affected, young animals are more prone to the condition.

2. Clinical findings. There is a transitory shifting leg lameness, generalized joint tenderness, and a stilted gait. Teeth may be loose, and later in the disease a bilateral firm enlargement of the facial bones above and anterior to the facial crests may be noted (big head disease).

3. Etiology and pathogenesis
   a. NSH occurs because of a compensatory increase in PTH secretion as a result of excessive phosphorus intake in the presence of normal or low serum calcium levels.
      (1) Hyperphosphatemia lowers blood calcium levels. Hypocalcemia stimulates PTH secretion, which returns blood calcium levels to normal or near normal.
      (2) Stimulation of PTH causes cellular hypertrophy and hyperplasia of the parathyroid glands.
         (a) PTH is involved in the fine regulation of **blood** calcium in mammals. Its direct effects are on bone, causing osteoclastic resorption, and on the kidney, causing calcium retention and phosphorus excretion. PTH also increases calcium absorption in the intestine.
         (b) Fibrous connective tissue is deposited when an excess amount of bone is removed, hence the name osteodystrophia fibrosa.
   b. The ingestion of excessive amounts of **oxalates** also may cause NSH. Oxalates decrease calcium absorption from the gut by forming insoluble complexes, which results in progressive hypocalcemia and PTH stimulation.

4. Diagnostic plan and laboratory tests. For a definitive diagnosis, serum and urine calcium and phosphate levels, percentage creatinine phosphate clearance, and serum alkaline phosphatase levels must be obtained. The calcium to phosphorus ratio in the ration also should be evaluated.

$$\frac{\text{Urinary } PO_4^-}{\text{Plasma } PO_4^-} \times \frac{\text{Plasma Cr}}{\text{Urinary}} \times 100 = \%CrPO_4^-$$

FIGURE 10-2. Calculation of the creatinine clearance ratio of phosphate ($\%CrPO_4^-$). *Cr* = creatinine; PO_4^- = phosphate.

a. **Hypocalcemia** and hyperphosphatemia occur very early, but values are often normal later in the course of the condition. Serum alkaline phosphatase (SAP) may be in the high normal range.
b. Changes in urine phosphates are more consistent. Calcium excretion decreases, whereas phosphate excretion in urine increases. These levels can be measured by the percentage urinary clearance of phosphates (Figure 10-2). Normal percentage creatinine phosphate clearance in horses is 0%–0.5%.

5. Differential diagnoses
   a. Lameness. A thorough lameness examination is necessary to rule out other causes of lameness.
   b. Neoplastic process of the facial bones. A biopsy and radiographs are necessary to rule out other causes of facial bone deformities.
6. Therapeutic plan. Dietary calcium should be increase and phosphorus intake should be decreased. Good alfalfa hay is high in calcium. Limestone (calcium carbonate) supplementation can also increase serum calcium. The clinical signs of lameness should disappear in 1–2 months after dietary correction. Facial swellings may never regress to normal.

C Pseudohyperparathyroidism (**PHT**)

1. Patient profile and history. This condition may be seen in older animals with a history of weight loss, polyuria and polydipsia, weakness, and gastrointestinal disturbances.
2. Clinical findings. PHT generally is associated with a neoplastic condition, specifically gastric adenocarcinoma and **lymphosarcoma.** Therefore, signs consistent with chronic diseases are evident.
3. Etiology and pathogenesis
   a. The pathogenesis of hypercalcemia associated with nonparathyroid tumors is not understood, but it is postulated that these tumors secrete PTH-like substances. Prostaglandins and their metabolites, vitamin D and non-vitamin D steroids. also could participate in **bone** resorption. The histopathology of the parathyroid glands indicates inactivity, atrophy, or both in response to the **hypercalcemia.**
   b. There are two mechanisms proposed for the **isosthenuria** that is seen in **hypercalcemia.**
      (1) Increased calcium in the renal cells interferes with the efficiency of the sodium pump, resulting in decreased sodium in the renal medulla and papilla. This leads to failure of the countercurrent exchange system.
      (2) Locally, increased calcium decreases the permeability of the distal convoluted tubules and collecting ducts to water.
4. Diagnostic plan. Serum calcium levels must be evaluated. Evidence of neoplasia should be sought. **Diagnostic workup** for neoplasia should include rectal examination, thoracic radiography, abdominocentesis, and gastric endoscopy. PTH levels will probably be normal in horses with PHT.
5. Laboratory tests. **Hypercalcemia** is the most consistent finding. A low serum phosphorus level may be present. There is an increase in SAP and isosthenuria.
6. Differential **diagnoses**
   a. Renal disease in horses may present as hypercalcemia, polyuria and polydipsia, and isosthenuria. Concomitant elevation of **BUN** and creatinine levels will indicate renal disease.

b. Ingestion of plants with vitamin D activity, such as *Cestrum diurnum* and *Solanum* malacoxylon, may cause hypercalcemia.
c. Primary hyperparathyroidism is rare in the horse.

7. Therapeutic plan and prognosis. Treatment is only palliative because of the associated neoplasia. Corticosteroids may be helpful to inhibit the action of PTH and prostaglandins, minimizing the hypercalcemia. Nonsteroidal anti-inflammatory drugs (NSAIDs) also inhibit prostaglandins. Because this disorder is associated with a poor prognosis, euthanasia is often considered.

D. Acute vitamin D_3 toxicosis

1. Patient profile and history. There is no age, sex, or breed predisposition with this disease. The client complains that the horse exhibits anorexia, weakness, limb stiffness, and weight loss.
2. Clinical findings. Affected horses exhibit depression, anorexia, weakness, and limb stiffness with impaired mobility. There may be polyuria and polydipsia.
3. Etiology and pathogenesis
   a. Etiology. Causes include accidental excess added to bulk feed, over-supplementation with parenteral vitamin D preparations, or the consumption of plants containing vitamin D-like substances. Two such plants, ***Cestrum diurnum*** and ***Solanum malacoxylon,*** are found in North America.
   b. Pathogenesis. Excessive exposure or administration of vitamin D leads to disseminated soft tissue mineralization.
      (1) Vitamin D exerts its effect primarily by increasing calcium and phosphorus absorption in the intestines and may enhance bone resorption. The cardiovascular system appears to be particularly affected.
      (2) Serum calcium levels fluctuate during the course of disease and may remain within normal limits. Therefore, serum calcium is an unreliable indicator of vitamin D toxicosis. Unlike renal disease and hyperparathyroidism, vitamin D toxicosis results in hyperphosphatemia.
4. Diagnostic plan. Obtain a thorough history and check serum calcium, phosphorus, and magnesium levels. Request a BUN, creatinine, urinalysis, and urinary clearance of phosphate. Perform a feed analysis if oral exposure is suspected.
5. Laboratory tests. There is usually a marked, persistent hyperphosphatemia. Hypercalcemia is a variable finding. BUN and creatinine are normal unless marked kidney mineralization has occurred.
6. Differential diagnoses
   a. Magnesium deficiency in the horse can present with similar morphologic lesions. Antemortem blood levels of calcium, phosphorus, and magnesium help differentiate the two problems.
   b. Chronic renal failure, neoplasia, and primary **hyperparathyroidism** can also cause hypercalcemia in horses and must be ruled out.
7. Therapeutic plan and prognosis. Withdraw any contaminated feed, and prevent over-supplementation. Rest and nursing care is the only recommended treatment. The feed supplier should be notified of the problem. The prognosis is poor for hones exhibiting cardiovascular abnormalities. In less severe cases, recovery may take 6 months or longer.

VII. ANHIDROSIS, or the inability to sweat, was once thought to result from poor acclimatization of horses native to cooler environments. It is now realized that anhidrosis affects even those horses native to hot, humid climates. Horses undergoing strenuous exercise (e.g., racing, polo, eventing) are affected as well as relatively idle broodmares and "backyard" pleasure horses.

A. Patient profile and history. Horses with this condition have a history of exercise intolerance and decreased appetite, and owners frequently notice animals sweat less than expected during periods of extreme heat and exercise.

B. Clinical findings. During episodes of exertion, the horse's rectal temperature and respiratory rate often are elevated. There may be no sweating or only patchy sweating. Chronically, there is a loss of body condition.

C. Etiology and pathogenesis

1. The etiology remains unknown. Cessation of sweating may be complete or partial because some horses maintain some sweating ability over the brisket, perineum, and under the mane. The disorder is most frequently recognized in hot, humid environments and seems to be precipitated by heat stress.
2. Pathogenesis. Proposed mechanisms of anhidrosis include the downregulation of sweat gland β_2-receptors in response to higher than normal concentrations of circulating epinephrine secondary to heat stress and also fatigue of sweat gland secretion resulting from prolonged demand. It is interesting to note that horses with anhidrosis do appear to have higher levels of circulating epinephrine than normal horses.

D. **Diagnostic** plan. Diagnosis is aided by the history of inadequate sweat production after appropriate stimulation. An intradermal epinephrine challenge may be applied. A total lack of sweat production at the site of injection is a poor prognostic sign.

E. **Laboratory** tests. There are no laboratory values of diagnostic significance.

F. **Therapeutic** plan. There is no consistent therapy to induce sweating. Oral supplementation of electrolytes is the most common therapy and meets with some success. Iodinated casein supplements have been tried with mixed results. Symptomatic therapy to promote heat dissipation should be employed. These techniques include air and water cooling, shade, and rest

G. Prevention. Moving horses to cooler climates helps.

STUDY QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE numbered answer or completion that is BEST in each case.

1. Which statement regarding equine Cushing's disease is correct?

(1) The hyperglycemia associated with equine Cushing's disease is usually insulin responsive.
(2) Surgery is the treatment of choice.
(3) A tumor of the pars distalis of the pituitary gland causes the clinical signs.
(4) A tumor produces excessive glucocorticoid, which decreases in response to a test dose of dexamethasone.
(5) Polyuria, hirsutism, and weight loss are common clinical findings.

2. An equine pituitary adenoma often presents with:

(1) colic and diarrhea.
(2) laminitis and chronic infections.
(3) excessive masculine or feminine behavior.
(4) a loud, pounding heart and renal failure.
(5) bone remodeling and pathologic fractures of long bones.

3. Which statement regarding equine pheochromocytoma is correct?Equine pheochromocytoma:

(1) if functional, causes increased epinephrine and norepinephrine secretion.
(2) is a tumor of the pars intermedia of the pituitary gland.
(3) causes anhidrosis.
(4) is a tumor most often restricted to female thoroughbreds.
(5) is most often treated by surgical removal.

4. Which statement correctly describes equine adrenal insufficiency?

(1) It causes paradoxically high serum cortisol levels.
(2) It has not been reported in mares.
(3) It is seen in horses that have received long-term glucocorticoid therapy.
(4) It can be diagnosed by a dexamethasone suppression test.
(5) It is best prevented by the use of anabolic steroids.

5. Which statement regarding equine hypothyroidism is correct?

(1) It is seen only in racehorses.
(2) It is not a life-threatening condition.
(3) Phenylbutazone administration may artificially increase serum thyroxine (T_4) values.
(4) It may cause horses to exhibit decreased endurance and stiffness.
(5) It is caused by a deficiency of vitamin D.

6. Goiter is best described by which of the following statements?Goiter:

(1) causes hypothyroidism due to iodine deficiency.
(2) is an immune-mediated thyroid disorder.
(3) results in a decrease in thyroid-stimulating hormone (TSH) production.
(4) is a condition restricted to North America.
(5) is of major clinical significance in weak and old animals.

7. Nutritional secondary hyperparathyroidism **(NSH)** causes which one of the following findings?

(1) Elevated serum phosphorus values
(2) A secondary decrease in parathyroid hormone (PTH) secretion
(3) Renal failure
(4) Lameness and enlargement of facial bones
(5) Decreased calcium absorption from the intestine

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8. The hypercalcemia seen in animals with equine pseudohyperparathyroidism (PHT) is related to:

(1) renal disease.
(2) pituitary disease.
(3) the ingestion of certain plants containing high calcium levels.
(4) vitamin C toxicity.
(5) tumors such as gastric adenocarcinoma or lymphosarcoma.

9. Acute vitamin D_3 toxicosis in the horse usually produces which one of the following signs?

(1) Blindness
(2) Marked, persistent hyperphosphatemia
(3) Renal failure
(4) An extremely low serum calcium
(5) Sweating and signs of colic

DIRECTIONS: The numbered item in this section is negatively phrased, as indicated by a capitalized word such as NOT, LEAST, or EXCEPT. Select the ONE numbered answer that is BEST.

10. The secretion of which of the following is NOT increased in cases of pituitary adenoma in horses?

(1) Melanocyte-stimulating hormone (MSH)
(2) β-Endorphins
(3) Adrenocorticotropic hormone **(ACTH)**
(4) Prolactin
(5) Corticotropin-like intermediate lobe peptide

ANSWERS AND EXPLANATIONS

1. The answer is 5 [III A]. The clinical findings of polyuria, hirsutism, and weight loss are associated with equine Cushing's disease. The pituitary tumor causing this disease is confined to the pars intermedia and secretes adrenocorticotropic hormone (ACTH) autonomously, resulting in adrenal gland hypertrophy and excess cortisol secretion. Therefore, the resultant hyperglycemia is not insulin responsive, and the high endogenous cortisol level does not respond to dexamethasone administration. Medical therapy may be attempted, but surgery is not an option.

2. The answer is 2 [III A 2 b]. In horses with pituitary adenoma, the high concentration of circulating endogenous steroids produced in response to excessive adrenocorticotropic hormone (ACTH) secretion from the pituitary tumor results in chronic infections and laminitis. None of the other sets of clinical findings (i.e., colic and diarrhea, excessive masculine or feminine behavior, a loud pounding heart and renal failure, or bone remodeling and pathologic fractures) can be attributed to equine Cushing's disease.

3. The answer is 1 [IV A]. Pheochromocytomas arise from the chromaffin cells of the adrenal medulla, and they will, if functional, secrete epinephrine and norepinephrine. Equine pheochromocytoma does not cause anhidrosis. Therapy is usually not attempted. The tumor is not restricted to female thoroughbreds.

4. The answer is 3 [IV B]. Equine adrenal insufficiency may be seen in a subset of race horses that have received long-term steroid agents to enhance performance. Endogenous cortisol levels are low because of adrenal gland atrophy. Therefore, horses do not respond to adrenocorticotropic hormone (ACTH) stimulation or further dexamethasone suppression.

5. The answer is 4 [V A]. In adult horses, hypothyroidism causes signs of lethargy, poor performance, and stiffness. Although often seen in racehorses, there is no breed or sex predilection. It may also be a disease of the unborn or neonate, in which case it is life threatening. It is diagnosed by measuring thyroxine (T_4) levels, which may be artificially lowered if the horse is receiving phenylbutazone. It may be caused by thyroid or pituitary disease.

6. The answer is 1 [V B 1–3]. Goiter is hypothyroidism due to iodine deficiency. It is seen worldwide and is of major significance in the young. It is not related to thyroid or pituitary disease or dysfunction.

7. The answer is 4 [VI B 2–3]. Nutritional secondary hyperparathyroidism (NSH) results from excessive phosphorus intake concurrent with low or normal calcium intake. The resultant parathyroid hormone (PTH) stimulation causes calcium absorption from the bone, calcium retention by the kidney, and phosphorus excretion. Bone remodeling occurs, causing lameness and enlargement of facial bones. Phosphorus levels may be elevated early in the course of the disease but are very often normal by the time clinical signs are present.

8. The answer is 5 [VI C 3]. Hypercalcemia in horses is often the first indication of a tumor (e.g., gastric adenocarcinoma, lymphosarcoma) and is termed pseudohyperparathyroidism (PHT).

9. The answer is 2 [VI D 2, 5]. Hyperphosphatemia is the most common laboratory finding with vitamin D_3 toxicosis. Blindness, renal failure, extreme hypocalcemia, sweating, and signs of colic do not occur with this condition.

10. The answer is 4 [III A 3 b]. Prolactin secretion is not increased in cases of equine pituitary adenoma. Melanocyte-stimulating hormone (MSH), β-endorphins, adrenocorticotropic hormone (ACTH), and corticotropin-like intermediate lobe peptide are derived from the pars intennedia of the pituitary gland and may be increased with equine Cushing's disease.